

EXHIBIT F



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

OCT 12 1990

Mr. James P. O'Donnell
Manager
Regulatory Affairs
Ethicon, Inc.
P.O. Box 151
Somerville, New Jersey 08876-0151

REGULATORY AFFAIRS

OCT 15 1990

RECEIVED

Re: N16374
PROLENE™, Polypropylene Nonabsorbable Suture

Dear Mr. O'Donnell:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) reclassified the nonabsorbable polypropylene surgical suture on July 5, 1990, effective on that date, from Class III into Class II (order enclosed). Notice of this reclassification will be announced in a future Federal Register notice. This letter constitutes notification that devices approved for commercial distribution under your PMA, N16374 and supplements 1 through 35, of your PMA, have also been reclassified into Class II.

FDA identified nonabsorbable polypropylene surgical suture as follows:

Nonabsorbable polypropylene surgical suture is a monofilament, nonabsorbable, sterile, flexible thread prepared from long-chain polyolefin polymer known as polypropylene and is intended for use in soft tissue approximation. The polypropylene surgical suture meets USP requirements as described in the USP Monograph for Nonabsorbable Surgical Sutures; it may be undyed or dyed with an FDA approved color additive; and the suture may be provided with or without a standard needle attached.

Accordingly, FDA has determined that your devices, as approved for marketing under your PMA and PMA supplements, are included in this generic type of device and are, therefore, reclassified into Class II. Although your devices were originally approved under an NDA/PMA application for commercial distribution, you may continue to market your devices subject to the general controls provisions of the Federal Food, Drug, and Cosmetic Act (act) and any performance standards promulgated under section 514 of the act. As such, any new device or any modification to your existing device(s) is subject to the premarket notification provisions of 21 CFR 807.81, and may require a determination of substantial equivalence in order to be marketed.

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If you have any questions, please contact Kenneth A. Palmer, Ph.D., at
(301) 427-1090.

Sincerely yours,

A handwritten signature in black ink, appearing to read "Robert L. Sheridan". The signature is fluid and cursive, with the first name "Robert" and last name "Sheridan" clearly distinguishable.

Robert L. Sheridan
Director
Office of Device Evaluation
Center for Devices and
Radiological Health

Enclosure



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1390 Piccard Drive
Rockville, MD 20850

JUL 5 1990

Mr. Walter S. Hennig
Vice President, Quality Functions
United States Surgical Corporation
150 Glover Avenue
Norwalk, Connecticut 06856

Re: Reclassification of Nonabsorbable Polypropylene
Surgical Suture, Docket Number 88P-0173

Dear Mr. Hennig:

INTRODUCTION

The Center for Devices and Radiological Health (CDRH) for the Food and Drug Administration (FDA) has completed its review of your reclassification petition for the nonabsorbable polypropylene surgical suture. FDA concludes that the generic type of device, nonabsorbable polypropylene surgical suture, and all devices substantially equivalent to this generic type, should be reclassified from class III into class II with a low priority for the development of a performance standard. This order, therefore, reclassifies nonabsorbable polypropylene surgical sutures into class II effective immediately.

FDA identifies the generic type of device the subject of this reclassification, as follows:

Nonabsorbable polypropylene surgical suture is a monofilament, nonabsorbable, sterile, flexible thread prepared from long-chain polyolefin polymer known as polypropylene and is indicated for use in soft tissue approximation. The polypropylene surgical suture meets USP requirements as described in the USP Monograph for Nonabsorbable Surgical Sutures; it may be undyed or dyed with an FDA approved color additive; and the suture may be provided with or without a standard needle attached.

As you know, on May 4, 1988, FDA filed the reclassification petition submitted by Advanced Biosearch Associates of Danville, California on your behalf requesting reclassification of nonabsorbable polypropylene surgical suture from class III into class II. The petition was submitted under section

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520(1) of the Federal Food, Drug and Cosmetic Act ("act"), 21 U.S.C. 360j(1), seeking reclassification under the procedures set forth in section 520(1)(2) of the act, 21 U.S.C. 360j(1)(2), and 21 CFR 860.136 of the agency's regulations.

Consistent with the act and the regulations, the agency consulted with the General and Plastic Surgery Devices Panel ("Panel") regarding the reclassification petition. The agency, by its September 28, 1988 letter and statements at the panel meeting, fully briefed the Panel about its obligations regarding the reclassification petition for nonabsorbable polypropylene surgical suture that was before it. The Panel, during an open public meeting on October 20, 1988, recommended that FDA reclassify nonabsorbable polypropylene surgical suture from class III into class II, and that FDA assign a high priority to the development of a performance standard for the generic type of device under section 514 of the act, although a performance standard need not be in place before reclassification is effective (Ref. 8 at page 55).

After reviewing all data in the petition and presented before the Panel, and after fully considering the Panel's recommendation and the views of the participants at the panel meeting, FDA, based on the information set forth in this letter, is ordering the reclassification of the generic type of device, identified on page 1, supra, from class III to class II.

RECLASSIFICATION PROCEDURE

Reclassification of nonabsorbable polypropylene surgical suture is governed by section 520(1) of the act, 21 U.S.C. 360j(1). The nonabsorbable polypropylene surgical suture is regulated as a class III device because prior to the Amendments it was subject to an approved "new drug" application submitted under section 505(b). See Section 520(1)(1)(A). Devices subject to "new drug" approvals prior to the Amendments are known as transitional devices and are automatically placed into class III to assure continuity of regulation.

Section 520(1)(1)(D), likewise, automatically classifies into class III a device that is "within a type of device described in subparagraph (A), (B), or (C) [of section 520(1)(1)] and is substantially equivalent to another device within that type." No time or other limitations narrow the scope of section 520(1)(1), nor is it suggested by the statute's text that anything other than all devices that fit within the scope of section 520(1)(1) are to be considered transitional, class III devices. Therefore, nonabsorbable polypropylene surgical sutures that are introduced well after the enactment date of the Amendments, which are substantially equivalent to a suture classified under section 520(1)(1)(A), are classified into class III under the authority of section 520(1)(1)(D).

Section 520(1)(2) of the act, which sets forth the procedures for reclassification of devices classified under section 520(1)(1), unambiguously applies to all devices classified under that section, and its scope is no more limited than that of section 520(1)(1). The statute's language is clear that section 520(1)(2) of the act is the exclusive means for reclassifying a device

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classified under section 520(1)(1). Nothing in the act suggests that transitional device reclassification should be initiated under any section of the act other than section 520(1)(2).

The act's premarket notification requirement demonstrates further that this proceeding is authorized by the transitional device reclassification provisions. If any person were to file a premarket notification under section 510(k) of the act, 21 U.S.C. 360(k), he would be required to identify:

The class in which the device is classified under section 513 or if such person determines that the device is not classified under such section, a statement of that determination and the basis for such person's determination that the device is or is not so classified (emphasis added). Id.

Clearly, nonabsorbable polypropylene surgical suture was not classified under section 513. Congress, as evidenced by the underlined portion of the above-quoted language, recognized that classification could occur outside of section 513. Section 520(1)(1) provides the only means of classifying a device outside of section 513 available under the act, and nonabsorbable polypropylene surgical suture was classified under the authority of that section. Accordingly, any person now bringing nonabsorbable polypropylene surgical suture to the market for the first time would be required to inform the agency in the context of section 510(k) of whether his nonabsorbable polypropylene surgical suture is substantially equivalent to a preamendment suture, as classified under section 520(1)(1), or a unique and, therefore, "new" suture as classified under section 513(f)(1).

For the nonabsorbable polypropylene surgical suture the subject of this reclassification proceeding, it is unchallenged that it was classified into class III under section 520(1)(1). Accordingly, since neither sections 520(1)(1) nor 520(1)(2) express any time restraints or other limitations regarding the acts of classification or reclassification of transitional devices, and since the Amendments, through premarket notification, intend that substantially equivalent devices, including transitional devices, be classified the same, I must conclude that the agency's position, that section 520(1)(2) describes the reclassification procedures for devices originally classified under section 520(1)(1), is reasonable and should be followed.¹

¹ The agency's understanding of the transitional device provision is consistent with the act and the agency's regulations, and is also supported by legislative history, stating:

[the] [o]ppportunity to petition [under the transitional device provisions] for reclassification to class II or I is afforded the manufacturer or importer of any device classified into class III as a result of [section 520(1)(1).]

H.R. Rep. No. 853, 94th Cong., 2d Sess., February 29, 1976 at 38.

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As the above discussion demonstrates, Congress intended to permit persons, who for the first time desire to manufacture or import transitional devices, the opportunity to seek reclassification under section 520(1)(2), notwithstanding the fact that reclassification was sought well after the passage of the Amendments. Moreover, U.S. Surgical, in our view and as the record shows, is an appropriate party to petition for reclassification under section 520(1)(2) in that the company intends to market nonabsorbable polypropylene surgical suture, and presently has received approval from FDA to export nonabsorbable polypropylene surgical suture to Italy, West Germany, France, The Netherlands and Switzerland (Ref. 150). Under these circumstances, U.S. Surgical, like any person submitting a premarket notification under section 510(k) seeking classification under section 520(1)(1), has standing to pursue reclassification under section 520(1)(2) from an automatic class III placement.

DECISION

After reviewing the publicly available literature in the record, the Panel's deliberation, and FDA's past actions regarding nonabsorbable polypropylene surgical suture, it is apparent to FDA that a class III designation for nonabsorbable polypropylene surgical suture constitutes overregulation.

By limiting the generic class, the subject of this order, to nonabsorbable polypropylene surgical suture, as defined on page 1, FDA, according to the record evidence, has limited this reclassification to nonabsorbable polypropylene surgical suture with the same or similar health risks. This approach is entirely consistent with FDA's definition of a generic type of device, see 21 CFR 860.3(i), and its view that "[t]he similarity of health risks is fundamental to the concept of classification by generic type of device," see 43 Fed. Reg. 32989, 32992 (July 28, 1978).

Additionally, U.S. Surgical has provided information in its petition to show that, despite variations in nonabsorbable polypropylene surgical suture materials and manufacturing processes, test methods exist to demonstrate whether any nonabsorbable polypropylene surgical suture is within the scope of the generic type of device identified in this order. Therefore, we believe that the nonabsorbable polypropylene surgical suture is well characterized and an appropriate candidate for reclassification.

As you have demonstrated, class II controls are appropriate to regulate nonabsorbable polypropylene surgical suture. Class II controls are indicated where class I controls alone are inadequate to reasonably assure a device's safety and effectiveness, and sufficient information exists to establish a performance standard to provide for such an assurance. See section 513(a)(1)(B) of the act, 21 U.S.C. 360c(a)(1)(B). As our discussion below demonstrates, the publicly available valid scientific evidence contained in the administrative record in this matter identifies the performance parameters and risks that define the safety and effectiveness of nonabsorbable polypropylene surgical suture. Also, valid scientific evidence in the record demonstrates the basis of a performance standard to control these parameters and risks and, thus, "sufficient information to establish a performance

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standard," (see section 513(a)(1)(B)), exists to classify nonabsorbable polypropylene surgical suture into class II.

A class II classification may occur with or without an actual standard being in place. Of importance is the fact that enough is known about the performance of nonabsorbable polypropylene surgical suture that the generic premarket clearance criteria of a performance standard constitute a more appropriate level of regulatory control than the agency's product by product premarket review, mandated by class III controls. Indeed, the data in the record show that when weighing benefits to the probable risk of illness or injury resulting from the use of nonabsorbable polypropylene surgical suture, class III controls are unnecessary to assure the device's safe and effective performance.

In granting your petition, FDA has relied on valid scientific evidence, as defined by 21 CFR 860.7(c)(2). The agency's regulations prescribe various types of evidence that may be valid scientific evidence, including, for example, well-controlled studies and reports of significant human experience with marketed devices. Although a well-controlled investigation is a component of valid scientific evidence, it is important to appreciate that such an investigation is but one type of evidence that can be relied upon by FDA to make classification and other regulatory decisions.

FDA firmly believes that end-product test methods are available to thoroughly evaluate nonabsorbable polypropylene surgical suture, and that publicly available valid scientific evidence supports this conclusion. The agency contrues section 514 of the act to sanction the use of end-product testing as a means of evaluating the properties and performance of a device. In that nonabsorbable polypropylene surgical suture is considered by the agency to be well characterized, and the record evidence supports this conclusion, and since valid scientific evidence shows the applicability of various end-product tests to the use of the suture in humans, we believe that class II controls provide a reasonable means, consistent with the act's purpose, to regulate nonabsorbable polypropylene surgical suture.

SCIENTIFIC BASIS

Suture Characterization

By definition, the nonabsorbable polypropylene surgical suture is well characterized. The suture is a monofilament, nonabsorbable, sterile, flexible thread prepared from long-chain polyolefin polymer known as polypropylene and is indicated for use in soft tissue approximation. The polypropylene surgical suture meets USP requirements as described in the USP Monograph for Nonabsorbable Surgical Sutures; it may be undyed or dyed with an FDA approved color additive; and the suture may be provided with or without a standard needle attached.

The nonabsorbable polypropylene surgical suture manufacturing process begins with production of the isotactic form of the polypropylene polymer wherein the attached methyl groups are arranged in a stereoregular

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configuration along one side of the "plane" described by a zig-zag carbon chain. It is produced in a solvent polymerization, using hydrocarbon solvent under pressure, at high temperatures and in the presence of a Zeigler-Natta catalyst which promotes the formation of the stereoregular isotactic form of the polypropylene polymer. The resulting insoluble isotactic polymer resin is subsequently purified by filtration and extraction to remove the catalyst, and then dried. Nonabsorbable polypropylene surgical suture may be left undyed (natural), or if desired, dyed with an FDA listed color additive in accordance with section 706 of the act.

The polypropylene resin is extruded at high temperature into polymer fibers of uniform diameter, and a specific multiple of their length are drawn or stretched to provide the necessary tensile properties. Nonabsorbable polypropylene surgical suture is ordinarily monofilamentous, and depending upon the final suture size desired, fibers of appropriate diameter and characteristics are produced. The processed thread is then cut to length, gauged to ensure uniform diameter and tensile strength in accordance with the requirements of United States Pharmacopeia (USP), appropriately packaged (with or without an attached needle), and sterilized to produce a finished suture (Refs. 7, 9, 29, 32, 65, 105, 133, 134 and 135).

Record data show that nonabsorbable polypropylene surgical suture's performance parameters and uses are well documented and understood, and that the generic type of device presents a reasonably uniform risk/benefit profile. Indeed the characteristics and composition of polypropylene are well-defined (Refs. 23, 24, 57, 58, 69, 72, 90, 91, 95, 113, 117, 120, 121, 126, 128-131, 134 and 135). Moreover, the performance parameters of existing nonabsorbable polypropylene surgical suture are well established (Refs. 9, 24, 29, 45, 50, 64, 121, 133, 134, 135 and 137) and the record shows the reasonably safe and effective use of nonabsorbable polypropylene surgical suture in humans (Refs. 17, 21, 33, 41, 42, 87, 95, 120 and 138).

The end product, given its indications for use, must have certain tensile strength characteristics (Refs. 9, 23, 28, 30, 34, 64, 74, 85, 89, 90, 91, 95, 113, 117, 120, 121, 126, 128, 129, 130, 133, 137 and 142). USP sutures, evaluated by uniform end-product testing, will perform successfully, notwithstanding different manufacturing processes (Refs. 7, 9, 64, 137, 24, 85, 133, 134 and 135), and will, among other things, have uniform tensile strengths. Since record data show that all nonabsorbable polypropylene surgical sutures present similar risks and performance characteristics (Refs. 9, 24, 29, 45, 50, 64, 121, 133, 134, 135 and 137), end product testing, in conjunction with other controls, will provide an appropriate means of reasonably assuring safe and effective nonabsorbable polypropylene surgical sutures.

In sum, the principal materials used to produce nonabsorbable polypropylene surgical suture is isotactic polypropylene polymer, and the physical characteristics of these polypropylene polymers are well understood. The USP Standard (Ref. 133 a-1), the American Society for Testing and Materials (ASTM) standards (Ref. 9 a-t) and other state-of-the-art test methods exist to evaluate and analyze the manufacturing process, composition, and physical, mechanical and biological properties of any nonabsorbable

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polypropylene surgical suture (Refs. 28, 30, 34, 88, 92, 110, 112, 113, 116-119, 130, 132 and 138). Nonabsorbable polypropylene surgical sutures present the same risks and performance parameters and can be standardized by end-product tests, and are regulable by the same or similar controls. Accordingly, the record shows that nonabsorbable polypropylene surgical suture constitutes a well characterized generic type of device.

Control of Suture Performance

The parameters that need control to provide reasonable assurance of safety and effectiveness for nonabsorbable polypropylene surgical suture are suture breakage, tissue inflammatory response, infection, and suture-related calculogenesis. A discussion of each parameter and the appropriateness of a class II classification for nonabsorbable polypropylene surgical suture, as supported by valid scientific evidence, follows.

1. Suture Breakage

The most important function of a suture is to successfully hold tissue together until healing is sufficiently complete so as to negate the need of the suture. Failure of a suture prior to a wound regaining adequate strength may result in wound dehiscence: a disruption of apposed wound surfaces, interfering with the normal healing process. Suture breakage may occur where there is premature loss of tensile strength (Refs. 4, 23, 29, 32, 42, 43, 44, 64, 70, 83, 90, 95, 115, 117, 121, 126, 128, 129, 130 and 149), due to unfavorable physiological wound site conditions (Refs. 11, 17, 18, 22, 33, 48, 66, 68, 74, 79, 80, 87, 102, 121 and 137), poor surgical technique (Refs. 11, 21, 66, 74, 77, 80, 83, 102, 107, 108, 109, 115, 117, 121 and 137), or improper use of the suture (id.). Importantly, the cumulative risk of nonabsorbable polypropylene surgical suture breakage is small, and its ability to function properly is uncontested.

The data in the record reveal that the incidence of wound dehiscence varies according to a number of factors, not all of which relate to suture breakage (Refs. 11, 17, 18, 48, 54, 66, 68, 74, 80, 81, 87, 107, 108, 109, 121 and 137). Of those wounds that dehisce, only a small fraction are attributable to suture breakage (Refs. 11, 17, 22, 48, 66, 74, 79, 109 and 121). It has also been shown that the incidence of wound dehiscence due to suture breakage occurs infrequently with nonabsorbable polypropylene surgical suture (Refs. 11, 22, 66, 74, 79, 108 and 109), and that the overall incidence of wound dehiscence with nonabsorbable polypropylene surgical suture is low (Refs. 22, 41, 68, 74, 79, 87 and 109).

The loss of tensile strength leading to suture breakage is a potential cause of failure of nonabsorbable polypropylene surgical suture in certain applications (Refs. 4, 32, 42, 70, 115 and 149). Retention of the suture's tensile strength is critical to the function of nonabsorbable polypropylene surgical suture. The record data show that the loss of tensile strength in vivo is primarily related to the oxidative degradation of the polypropylene polymer (Refs. 4, 29, 32, 42, 43 and 44) and that the polymer's degradation proceeds slowly and is generally not considered clinically significant under most circumstances of use (Refs. 1, 4, 42, 121 and 149). The rate and extent

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of oxidative degradation vary according to exposure to ultraviolet radiation, and may make the use of the suture in the eye questionable (Refs. 4, 32, 42, 70 and 149). Oxidative enzyme activity and the type of tissue at the wound site, e.g., actively metabolizing tissues, tissues with high oxygen concentration, and inflammation may also contraindicate the suture for certain applications (Refs. 4, 32, 42, 43, 44, 70 and 149).

The patient's health and response to the suture material may affect wound healing (Refs. 11, 17, 18, 48, 66, 74, 80, 81, 87, 107, 108, 109 and 121). Patients whose health has been compromised or weakened by poor nutrition, advanced age, obesity, uncontrolled diabetes, infection, anemia, or with certain forms of cancer, may exhibit delayed wound healing (Refs. 11, 17, 18, 48, 66, 74, 80, 81, 87, 107, 108, 109 and 121) which may increase the likelihood of suture failure. Although some of these factors have been shown experimentally to delay increases in wound strength, a nonabsorbable suture, such as nonabsorbable polypropylene surgical suture, may be preferred over absorbable sutures due to the suture's continuous support of tissues (Refs. 17, 48, 66, 74, 108, 121 and 137).

The appropriate use of nonabsorbable polypropylene surgical suture is important in defining its performance. The record shows that nonabsorbable polypropylene surgical suture has been successfully used in various wound sites and conditions in humans (Refs. 17, 21, 33, 41, 42, 87, 95, 120 and 138). Although, wound dehiscence is most significant in wound closures involving sites which can undergo expansion, stretching, or distention, such as the abdomen, chest, and joints, nonabsorbable polypropylene surgical suture may be the suture of choice due to its continued support of tissues (Refs. 11, 17, 18, 22, 33, 48, 66, 74, 79, 80, 81, 87, 102, 108, 121 and 137). Using nonabsorbable polypropylene surgical suture to close certain wounds has documented advantages related to the physical properties of the suture (Refs. 11, 22, 33, 66, 74, 79, 80, 81, 87, 108 and 121).

Surgical technique also affects the performance of sutures, including nonabsorbable polypropylene surgical suture. Improper closure technique can result in tissue separation and failure of the wound to heal. The factors relating to the wound closure technique that contribute to wound dehiscence include the tightness with which sutures are tied, suture knot security, the adequacy of tissue bites to allow for adequate wound expansion due to distention and damage to the suture during placement (Refs. 11, 17, 18, 21, 23, 48, 57, 58, 64, 66, 69, 74, 77, 79, 83, 87, 95, 102, 107, 108, 109, 115, 117, 120, 121, 129 and 130).

The critical parameter of tensile strength can be controlled by standard in vitro test methods and animal testing. The tensile strength of nonabsorbable polypropylene surgical suture before implantation and after explantation may be measured in a motor-driven tensile strength machine using equipment and procedures described in the USP (Refs. 133, 134 and 135). Moreover, various American Society for Testing and Material (ASTM) tests to evaluate suture strength exist and include, for example, yarn breaking load, breaking tenacity in loop/knot configuration, single textile fiber tensile strength, and in vitro strength loss and material degradation tests (Refs. 9, 134 and 135). Finally, to determine the effects of implantation of

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nonabsorbable polypropylene surgical suture upon tensile strength, various in vitro and in vivo methods used by Salthouse (Refs. 116 and 117), Postlethwait (Ref. 110), and others (Refs. 30, 64, 128, 129 and 130), which compare the tensile strength of various absorbable and nonabsorbable sutures, show a suture's performance characteristics.

The various evaluative methods included in the above references are applicable to the safe and effective use of nonabsorbable polypropylene surgical suture in humans in that sutures that have been successfully used in humans are routinely evaluated with these evaluative methods (Refs. 17, 21, 33, 41, 42, 87, 95, 120 and 138). Importantly, the time necessary for wound healing in various sites in humans is known (Refs. 2, 3, 5, 6, 13, 14, 19, 20, 24, 25, 27, 38, 39, 49, 50, 52, 60, 61, 63, 74, 75, 76, 77, 78, 98, 101, 103, 107, 114, 116, 121, 124, 127, 137 and 143), and the above methods permit a determination of whether sufficient suture tensile strength will be present over time to assure a successful result at any given wound site.

Also, many of the above-identified performance parameters and risks can be adequately controlled by labeling disclosures which may be incorporated into a class II standard or required by the class I misbranding controls, which include, among other things, the requirement of adequate directions for use. Disclosures can be made which contain warnings against the use of nonabsorbable polypropylene surgical suture in certain conditions, such as intracamerally in the eye. Also, risks may be avoided by disclosing in labeling that users must be familiar with surgical procedures and techniques involving nonabsorbable polypropylene surgical suture before using it to close wounds.

2. Tissue Inflammatory Response

A tissue inflammatory response is an acute or chronic, localized reaction. Many factors may cause a tissue inflammatory response, including trauma attributed to the implantation of a suture, (Refs. 17, 29, 50, 66, 89, 110, 116, 117, 121, 125, 126 and 137), and foreign body reactions to the suture material (Ref. 74, 87, 107, 119, 121, and 123).

Various studies have documented that an early tissue inflammatory reaction results from the trauma of inserting sutures and does not occur as a result of a reaction to suture material (Refs. 82, 84 and 144). When the suture is placed within tissue with little or no trauma, no inflammatory cell response results, suggesting the conclusion that the body's nonspecific response to tissue injury induces the appearance of inflammatory cells usually seen immediately after suturing (Refs. 31, 87, 107, 119, 146 and 147). The initial reaction of tissues after suturing reflects the amount of injury inherent in the process, and that injury typically is the same for all sutures 5 to 7 days after suturing (Refs. 17, 111, 121, 126, 127 and 137).

The inflammatory response observed beyond 5 to 7 days postoperatively is dependent upon the nature of the specific suture material employed. Specifically, synthetic materials elicit a lesser response than sutures of natural origin (Refs. 29, 110, 116, 117, 119, 121 and 136), and nonabsorbable polypropylene surgical sutures elicit a milder response than absorbable

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sutures (Refs. 37, 89, 119, 126, 127 and 137). Additionally, fine gauge sutures provoke a lesser response than large diameter sutures because of their lesser mass and therefore lesser amount of implanted foreign material (Refs. 50 and 136).

Record data show that nonabsorbable polypropylene surgical suture elicits a very mild chronic inflammatory response (Refs. 29, 89, 110, 116, 117, 119, 121, 126, 127 and 137), and because it is ordinarily monofilamentous, this response is among the most benign elicited by any suture material (Ref. 110). Following the initial inflammatory phase, a mild chronic tissue response to nonabsorbable polypropylene surgical suture is seen which is typically characterized by gradual formation of a fibrous encapsulation of the suture with little or no persistent cellular response (Refs. 87, 107, 119, 146 and 147). The chronic tissue inflammatory response to nonabsorbable polypropylene surgical suture is observed to be mild, and less than that elicited by certain other sutures (Refs. 87, 107, 119, 146 and 147) even though the chronic inflammatory response to nonabsorbable polypropylene surgical suture may be associated with granuloma formation in certain circumstances and wound sites (Refs. 74, 87, 107, 119, 121 and 123).

Because of the biocompatibility of the synthetic polypropylene material, nonabsorbable polypropylene surgical suture has not been associated with allergic and antigenic reactions. Although the manufacturing process may introduce impurities and residues that can cause tissue inflammatory response, numerous well-established biocompatibility tests provide methods to evaluate a suture's inflammatory potential, including USP tests for impurities and residues, or other state-of-the-art analytical methods (Refs. 8, 9, 10, 12, 51, 53, 62, 65, 72, 86, 93, 96, 97, 104, 106, 112, 132, 133, 134, 145 and 148).

In summary, the risk of early tissue inflammation resulting from trauma is related to the user technique and is no greater for nonabsorbable polypropylene surgical suture than for other suture material. Further, the foreign body response to nonabsorbable polypropylene surgical suture is mild in nature and, therefore, the suture in some circumstances may be preferred to other nonabsorbable sutures. Appropriate labeling disclosures related to tissue inflammation may indicate that all nonabsorbable sutures present an inflammatory response and that nonabsorbable polypropylene surgical suture is less pronounced than that of other nonabsorbable sutures. Moreover, to the extent the manufacturing process may cause residues that introduce a potential for allergic or antigenic reaction, which otherwise is not present with the nonabsorbable polypropylene surgical suture, well-established biocompatibility tests, as part of a standard, exist to evaluate the suture's inflammatory potential.

3. Infection

Although polypropylene surgical suture is manufactured and marketed as a sterile device in accordance with voluntary standards for sterility (Refs. 7, 9, 133 and 134), it, nonetheless, may exacerbate the effects of an existing wound infection, because of its composition, physical configuration, and duration of contact with tissue (Refs. 15, 16, 29, 31, 35, 36, 40, 45, 48, 50,

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55, 56, 66, 73, 122, 123, 125, 127 and 141). It has been established that the presence of suture material in a wound increases the wound's susceptibility to infection where the suture serves as a conduit for the mechanical transport of bacteria (Refs. 15, 29, 31, 36, 40, 50, 55, 66, 73, 108, 123, 125, 127, 136 and 139). Also, materials which permit the adherence of the largest amount of bacteria cause the greatest degree of post-surgical infection (Refs. 31, 36, 56, 73 and 125). Indeed, a comparative study of 10 sutures demonstrates that the physical configuration and chemical nature of various suture materials, their coating mechanisms, and the duration of contact between the sutures and bacteria, contribute to the bacterial adherence of the suture. (Ref. 31). The physical configuration of suture material is found to correlate positively with the degree to which sutures aggravate infected wounds (*id.*), and the use of suture coatings do not appear to reduce the suture-related infection rate (Refs. 36, 45, 50, 55, 123 and 127).

In the presence of infection or contamination, all sutures appear to potentiate the wound infection (Refs. 29, 45, 48, 50, 123 and 127). While nonabsorbable polypropylene surgical suture is not unique in its potential to exacerbate infection, it does appear to carry a somewhat lesser risk than other sutures in this regard (Refs. 16, 32, 40, 55, 95, 121, 123, 126, 138 and 170). The choice of suture material may, therefore, be critical when closing a wound in the presence of infection or potential infection. Because the nonabsorbable polypropylene surgical suture presents somewhat of a lesser risk than other sutures to potential infection, it is a suture of choice for infected wounds or contaminated wounds that present a substantial risk of infection (Refs. 16, 29, 32, 35, 40, 45, 48, 55, 73, 95, 123, 126, 138, 139, 140 and 141).

In summary, since suture selection may be a critical factor in avoiding the exacerbation of an infection, adequate labeling for the nonabsorbable polypropylene surgical suture, as part of a standard, could state that it is a suture of choice in closing infected or contaminated wounds.

4. Calculogenesis

Nonabsorbable polypropylene surgical suture, like other suture material, has been shown to be a nidus for calculogenesis when in contact with salt solutions of the bladder and biliary tract (Refs. 47, 66, 107 and 137). Calculi formation occurs on other natural and synthetic sutures in the bladder, and calculi formation appears to be dependant on the length of time the suture is in contact with urine in the bladder (Refs. 18, 47, 107, 117, and 137). Studies also report that nonabsorbable polypropylene surgical suture, and other sutures, when exposed to salt solutions in the common bile duct have been associated with stone formation (Refs. 18, 60 and 137).

The risk of calculogenesis resulting from implantation of nonabsorbable polypropylene surgical suture in either the urinary or biliary tract is related to the length of time the suture is in contact with a salt solution in those tracts. The risk of calculogenesis with nonabsorbable polypropylene surgical suture is typical of that associated with all nonabsorbable sutures. Thus, adequate labeling as part of a standard, can control this risk by stating that it is inadvisable to place nonabsorbable polypropylene surgical

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suture, or for that matter, any suture, in contact with salt solutions in the body's urinary and biliary tracts.

Based on the information presented above, it can be concluded that nonabsorbable polypropylene surgical suture is well characterized and that there is sufficient publicly available valid scientific evidence to demonstrate that a performance standard can be established and used, in combination with the general controls, to provide reasonable assurance of the safety and effectiveness of nonabsorbable polypropylene surgical suture. For control of suture breakage, in particular, for control of suture tensile strength, a standard can assure device safety and effectiveness. See pages 8-9. Likewise, suture-related tissue inflammatory response can be controlled by a performance standard. See page 10.

The act's general controls also make a substantial contribution to the regulation of nonabsorbable polypropylene surgical suture. Manufacturing processes for nonabsorbable polypropylene surgical suture are and will be subject to FDA's Good Manufacturing Practice regulations, and the act's adulteration provisions. Moreover, labeling warnings and disclosures identified throughout this order will provide sufficient control of various nonabsorbable polypropylene surgical suture-related performance parameters or risks to reasonably assure the suture's safe and effective use.

PRIORITY FOR THE DEVELOPMENT OF A STANDARD

While valid scientific evidence demonstrates that a performance standard may be written to control the material, composition, and physical characteristic of this generic type of device in order to reasonably assure its safety and effectiveness, one is not immediately needed. Existing devices, within the generic type covered by this order, typically conform to voluntary standards, including USP standards for nonabsorbable surgical suture. Moreover, nonabsorbable polypropylene surgical suture, as currently manufactured, has established a reasonable record of safe and effective use. The basic properties, principles of manufacture, and appropriate indications and contra-indications for use of nonabsorbable polypropylene surgical suture are well-established, both scientifically and clinically, as documented in publicly available information contained in the petition (Refs. 28, 39, 63, 64, 75, 76, 90, 98, 107, 121, 126 and 134).

In this matter, significant publicly available information indicates that existing nonabsorbable polypropylene surgical sutures are generally safe and effective (Refs. 24, 29, 39, 63, 75, 76, 80, 85, 98, 107, 110, 117, 121 and 127). Thus, FDA concludes that development of a mandatory performance standard is not immediately necessary to protect the public health.

State-of-the-art test methods are well-established to evaluate and analyze the structure, composition, physical, chemical, mechanical, physicochemical and biological properties of any nonabsorbable polypropylene surgical suture to allow a precise determination to be made of the relative safety and effectiveness of marketed nonabsorbable polypropylene surgical sutures and those intended for commercial distribution. Thus, the determination of

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comparable safety and effectiveness of future nonabsorbable polypropylene surgical suture and marketed sutures can be made in the context of a premarket notification under section 510(k) of the act, 21 USC 360(k).

FDA, therefore, respectfully disagrees with Panel's recommendation that the promulgation of a mandatory performance standard be a high priority. FDA concludes that development of a mandatory performance standard should be a low priority because the establishment of a regulatory standard is not immediately necessary to protect the public health.

CONCLUSION

Based on the information provided in the petition and presented at the panel meeting, and the information submitted to the administrative record, FDA concludes that the generic type of device, nonabsorbable polypropylene surgical suture, should be reclassified from class III to class II with a low priority for the development of a performance standard.

Sincerely yours,



Robert L. Sheridan
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Enclosure: References

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